

# Effect of Intravenous Paracetamol on Postoperative Morphine Requirements in Neonates and Infants Undergoing Major Noncardiac Surgery

## A Randomized Controlled Trial

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**T**HE TREATMENT OF PAIN IN young children has improved after the publications by Anand et al<sup>1,2</sup> in 1987 that made clear that neonates have well-developed nociceptive pathways and therefore are capable of experiencing pain. Because untreated pain is both an unwanted experience and ultimately may lead to adverse consequences,<sup>3-6</sup> opioids were introduced and have been used ever since.<sup>7</sup> Opioid therapy, however, is associated with adverse effects, in particular respiratory depression.<sup>8</sup> Researchers, therefore, are in search of alternative analgesic regimens in neonates and infants.<sup>9</sup>

Paracetamol (acetaminophen) has been proposed as an alternative. To the best of our knowledge, only 2 studies have evaluated the opioid-sparing effect of paracetamol as add-on medication in postoperative neonates and in-

**Importance** Continuous morphine infusion as standard postoperative analgesic therapy in young infants is associated with unwanted adverse effects such as respiratory depression.

**Objective** To determine whether intravenous paracetamol (acetaminophen) would significantly (>30%) reduce morphine requirements in neonates and infants after major surgery.

**Design, Setting, and Patients** Single-center, randomized, double-blind study conducted in a level 3 pediatric intensive care unit in Rotterdam, the Netherlands. Patients were 71 neonates or infants younger than 1 year undergoing major thoracic (noncardiac) or abdominal surgery between March 2008 and July 2010, with follow-up of 48 hours.

**Interventions** All patients received a loading dose of morphine 30 minutes before the end of surgery, followed by continuous morphine or intermittent intravenous paracetamol up to 48 hours postsurgery. Infants in both study groups received morphine (boluses and/or continuous infusion) as rescue medication on the guidance of the validated pain assessment instruments.

**Main Outcome Measures** Primary outcome was cumulative morphine dose (study and rescue dose). Secondary outcomes were pain scores and morphine-related adverse effects.

**Results** The cumulative median morphine dose in the first 48 hours postoperatively was 121 (interquartile range, 99-264)  $\mu\text{g}/\text{kg}$  in the paracetamol group ( $n=33$ ) and 357 (interquartile range, 220-605)  $\mu\text{g}/\text{kg}$  in the morphine group ( $n=38$ ),  $P<.001$ , with a between-group difference that was 66% (95% CI, 34%-109%) lower in the paracetamol group. Pain scores and adverse effects were not significantly different between groups.

**Conclusion and Relevance** Among infants undergoing major surgery, postoperative use of intermittent intravenous paracetamol compared with continuous morphine resulted in a lower cumulative morphine dose over 48 hours.

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ants. One, a randomized controlled trial of rectal paracetamol in neonates aged 0 to 2 months undergoing major non-

cardiac thoracic or abdominal surgery, failed to show such an effect.<sup>10</sup> The other, however, demonstrated a fentanyl-

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**For editorial comment see p 183.**

sparing effect of intravenous paracetamol in infants aged 6 to 24 months following ureteroneocystostomy.<sup>11</sup> The discrepancy between these studies may be explained by the different paracetamol formulations. Neither study directly compared the analgesic effect of morphine with that of paracetamol as primary analgesic. It could be argued that intravenous paracetamol with an option for rescue morphine boluses may further reduce postoperative opioid consumption.<sup>12</sup>

We performed a randomized controlled trial in infants who had undergone major abdominal and thoracic (noncardiac) surgery. The aim of this trial was to determine if intravenous paracetamol would reduce the cumulative morphine dose needed to provide adequate analgesia by at least 30%.

## METHODS

### Patients

In this single-center, randomized, double-blind study, all children younger than 1 year undergoing major thoracic (noncardiac) or abdominal surgery between March 2008 and July 2010 at the Erasmus MC–Sophia Children's Hospital in Rotterdam, the Netherlands, were eligible for inclusion. Inclusion criteria were post-conceptual age of 36 1/7 week or older to 1 year of age; body weight greater than 1500 g; and undergoing major thoracic (noncardiac) or abdominal surgery.

Exclusion criteria were extracorporeal membrane oxygenation treatment; neurologic dysfunction, hepatic dysfunction, or renal insufficiency; prenatal or postnatal administration of opioids or psychotropic drugs (antiepileptics, benzodiazepines, antidepressants) for more than 24 hours; known allergy to or intolerance for paracetamol or morphine; and administration of opioids in the 24 hours prior to surgery.

The study was approved by the Erasmus MC ethics review board; written informed consent from parents or legal representatives was obtained.

### Study Design

Patients were randomized to receive either morphine or paracetamol post-

operatively. When patients were randomized to receive paracetamol (30 mg/kg per day in 4 doses), a placebo infusion of normal saline was administered continuously at the same rate as an equivalent morphine infusion. When randomized to receive morphine (patients aged  $\leq 10$  days, 2.5  $\mu\text{g}/\text{kg}^{1.5}$  per hour; patients aged 11 days to 1 year, 5  $\mu\text{g}/\text{kg}^{1.5}$  per hour), normal saline was administered 4 times daily as placebo in a volume similar to the intravenous paracetamol dose. Placebos could not be distinguished from the active study drug in color, odor, or viscosity. The morphine dosing schedule accounts for age-related changes in morphine clearance in addition to weight; eg, a 10-kg infant would receive 16  $\mu\text{g}/\text{kg}$  per hour, a 5-kg infant, 11  $\mu\text{g}/\text{kg}$  per hour; an infant weighing 3 kg and older than 10 days, 9  $\mu\text{g}/\text{kg}$  per hour; and an infant weighing 3 kg and aged 10 days or younger, 4  $\mu\text{g}/\text{kg}$  per hour.<sup>13,14</sup> For comparison, international guidelines<sup>15</sup> suggest 10 to 30  $\mu\text{g}/\text{kg}$  per hour.

In both study groups, rescue morphine (patients aged 0 through 10 days, 10  $\mu\text{g}/\text{kg}$ ; patients aged 11 days to 1 year, 15  $\mu\text{g}/\text{kg}$ ) was administered whenever Numeric Rating Scale-11 (NRS-11) and COMFORT-Behavior Scale (COMFORT-B) scores indicated pain. Rescue doses were administered every 10 minutes when needed, with a maximum of 3 per hour. If pain persisted, a continuous morphine rescue infusion was started at 1.25  $\mu\text{g}/\text{kg}^{1.5}$  per hour (patients aged 0 through 10 days) or 2.5  $\mu\text{g}/\text{kg}^{1.5}$  per hour (patients aged 11 days to 1 year), after a loading dose of 100  $\mu\text{g}/\text{kg}$ . When patients then still needed rescue morphine 3 times per hour, the infusion dose was doubled. Eventually, if pain persisted in spite of the rescue morphine boluses and the continuous morphine infusion at a maximum dose, fentanyl was started. If pain decreased, as documented by NRS-11 scores below 4 for more than 12 hours, morphine dosage was reduced by 50%.

In case of discomfort (COMFORT-B score  $\geq 17$  and NRS-11 score  $< 4$ ), midazolam was started.

### Assessments

To assess pain, the patient's nurse performed pain assessment every 8 hours and additionally when behavior suggested pain. Pain and distress assessments were performed using the NRS-11 and COMFORT-B scale, respectively, which are extensively validated scales in neonates and infants.<sup>16-20</sup>

When using the NRS-11, caregivers rate the observed pain on a scale from 0 to 10, where 0 represents "no pain" and 10 represents "the worst pain possible," using whole numbers (11 integers including zero). The COMFORT-B scale consists of 6 behavioral items<sup>18</sup>: alertness; calmness/agitation; crying or, in case of artificial ventilation, breathing reaction; physical movements; muscle tone; and facial tension. A trained intensive care nurse observes a patient for a 2-minute period, during which all items are assessed on a 5-point numerical scale (1-5). The most distressed behavior during the 2-minute period is scored, resulting in a total score of 6 to 30.

Pain is indicated with an NRS-11 score of 4 or greater. Distress is indicated with an NRS-11 score less than 4 and COMFORT-B score of 17 or greater. Interrater reliability had been established on the basis of 10 paired observations with a nurse already trained. A linear weighted Cohen  $\kappa$  greater than 0.65 was found for all nurses. The median scored linear weighted  $\kappa$  for the COMFORT-B scale was 0.79 (interquartile range [IQR], 0.72-0.86).

The Surgical Stress Score was computed by the surgeon; scores range from 3 to 22, with higher scores indicating more severe surgical stress.<sup>21</sup>

### Randomization and Blinding

Patients had an equal probability of assignment to study groups. Stratified randomization was used in combination with random permuted blocks. Initially, we stratified for 4 age groups: 0 to 10 days, 11 days to 3 months, 3 to 6 months, and 6 to 12 months. A hospital pharmacist carried out computer randomization in advance, and codes were safely stored. Inclusion numbers

for the second, third, and fourth age groups were falling behind after 9 months of inclusion (18 included in the first group, 2 in the second, 11 in the third, 3 in the fourth). We then decided to randomize into 2 age groups: 0 through 10 days and 11 days to 1 year, because major changes in pharmacokinetics of morphine are to be expected in the first 10 days of life, with relatively minor changes thereafter.<sup>13</sup> A new randomization schedule was computer generated by the same pharmacist. Only the pharmacist had access to group allocation during the study period, for preparation of study medication.

### Standardized Anesthesia

Anesthesia was induced by thiopental (3-5 mg/kg) or by inhalation with sevoflurane in air/oxygen mixture. Fentanyl (2-5  $\mu$ g/kg) was administered before tracheal intubation, with a cumulative total dose of 5  $\mu$ g/kg before the surgical procedure. Tracheal intubation was facilitated with *cis*-atracurium (0.15 mg/kg), except for rapid-sequence inductions, for which succinylcholine (2 mg/kg) was administered. Anesthesia was maintained with oxygen/air and isoflurane, titrated to an end tidal concentration of 0.8% to 1.2%. Extra doses of fentanyl (2  $\mu$ g/kg) were administered when heart rate or mean arterial blood pressure was 10% or more above baseline values. Perioperative fluids were given in a standardized way, and normoglycemia was maintained alongside normothermia (35.5°C to 37°C).

All patients received a loading dose of morphine (100  $\mu$ g/kg) 30 minutes before the anticipated end of the surgical procedure. Postoperatively they were directly transferred to the intensive care unit, where study medication was started within 5 minutes after arrival. An attempt to extubate all patients was made in the operating room. When extubation was not feasible in the operating room, patients were extubated in the intensive care unit as soon as spontaneous breathing was sufficient, per the attending physician's judgment.

### Study End Points

The primary end point was the cumulative morphine dose, ie, the sum of the intraoperative loading dose, the morphine study dose, and the rescue morphine doses.

Secondary end points were morphine rescue dose in micrograms per kilogram in the first 48 hours postoperatively, number of extra rescue morphine doses and infusions (each rescue dose or rescue dose in combination with a rescue infusion start or increase counted as one), number of patients receiving rescue doses, average NRS-11 and COMFORT-B scores, and morphine-related adverse effects.

Morphine-related adverse effects were defined as (1) need for mechanical ventilation, reintubation, or both; (2) apnea, defined as oxygen saturation by pulse oximetry less than 94% or respiratory rate less than 20 breaths/min longer than 30 seconds; (3) naloxone administration; (4) bradycardia, defined as heart rate less than 80 beats/min and more than 30 seconds per episode other than attributable to or directly related to the disease or operation; (5) hypotension, defined as need for vasoactive medication or additional fluid boluses; (6) seizures, when other causes could be ruled out; (7) gastrointestinal adverse effects, defined as ileus signs or need for antiemetics or laxatives; and (8) urinary retention.

### Clinical Data Collection

Clinical data collected were sex, age at surgery, body weight, duration and type of surgery (thoracic or abdominal), co-medication, mechanical ventilation postoperatively, severity-of-illness scores (Pediatric Risk of Mortality 3, for which higher scores indicate higher risk of mortality [maximum score, 74], and Pediatric Index of Mortality 2, for which the score [%] indicates the predicted death rate).<sup>22,23</sup>

### Statistical Methods

**Power Analysis.** We considered a 30% reduction in cumulative morphine dose (from 480 [SD, 200]  $\mu$ g/kg per 48

hours to 336  $\mu$ g/kg per hour, based on previous data)<sup>24</sup> in the intravenous paracetamol group compared with the morphine group clinically relevant. Using these assumptions, the number of patients required in each group equaled 32, as shown by a power analysis in which the  $\alpha$  level of significance was fixed at .05 (2-tailed) and the  $\beta$  level was fixed at .20. Considering a dropout rate of 15%, 37 patients per group were needed.

**Interim Evaluation.** The study was to be discontinued when more than 18 patients would have needed a rescue morphine infusion (ie, 3 doses of morphine and start of background morphine). This cutoff was chosen because in this situation both intravenous paracetamol and the morphine starting dose were inadequate as primary analgesia.

The pharmacist and the statistician performed this interim evaluation after inclusion of 20 patients; the pharmacist, statistician, and investigators remained blinded.

**Statistical Analysis.** Descriptive statistics served to compare clinical characteristics. The Kolmogorov-Smirnov test served to assess distribution of the variables. Groups were compared using *t* test or Mann-Whitney test. Odds ratios and 95% CIs were estimated to compare groups with respect to adverse events as dichotomous variables (yes/no). Other proportions were compared by using  $\chi^2$  tests with continuity correction or using Fisher exact test when appropriate. Level of significance was set at .05, 2-sided.

Statistical analyses were performed using SPSS version 17.0 (SPSS Inc).

## RESULTS

### Patient Characteristics

We initially enrolled 74 patients. However, informed consent was withdrawn in 1 patient before start of the study procedure, 1 patient eventually did not undergo major surgery (no intussusception present at laparoscopy), and 1 patient had blood test results obtained just before surgery that

revealed abnormal liver function (FIGURE 1).

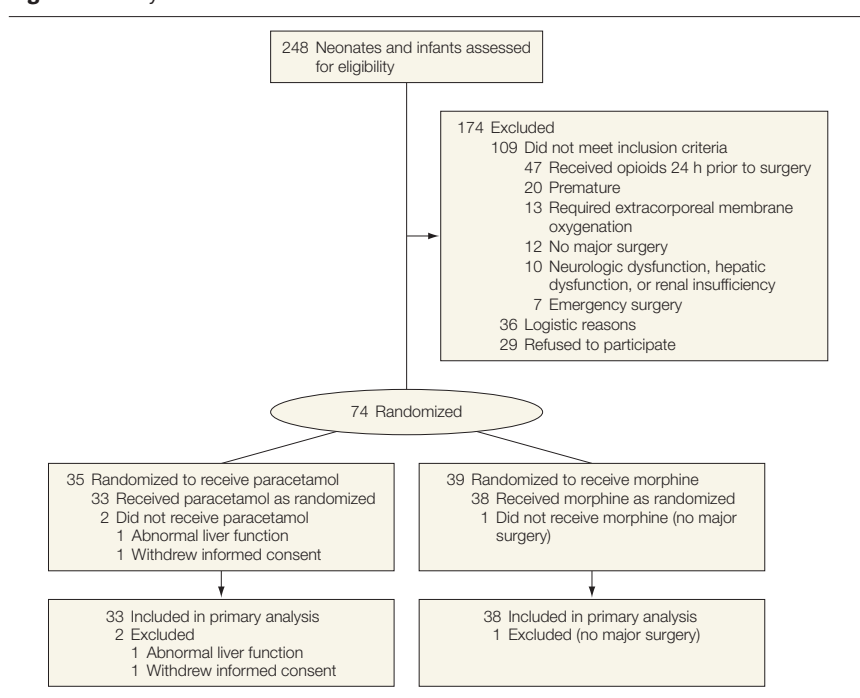
The characteristics of the remaining 71 patients did not differ significantly between the paracetamol and morphine groups (TABLE 1). The most frequent surgical procedures were clo-

sure of congenital diaphragmatic hernia and repair of intestinal atresia and esophageal atresia.

One patient with gastroschisis in the paracetamol group underwent additional surgery for bowel necrosis. This patient postoperatively received ve-

curonium, on account of which the NRS-11 and the COMFORT-B could not be applied, and therefore the study medication was terminated and replaced by morphine after 19 hours and cumulative morphine dose was calculated for the first 48 hours postoperatively (intention-to-treat).

**Figure 1.** Study Flow



**Table 1.** Patient Characteristics

Characteristic	No. (%)		P Value
	Paracetamol (n = 33)	Morphine (n = 38)	
Sex			
Male	18 (54.5)	26 (68.4)	.23
Female	15 (45.5)	12 (31.6)	
Age at surgery, median (IQR), d	5 (1.5-64.5)	20 (1.8-87.5)	.50
Age, d			
≤10	17 (51.5)	18 (47.4)	.73
>10	16 (48.5)	20 (52.6)	
Weight, mean (SD), kg	3.8 (1.3)	4.4 (2.0)	.17
Duration of surgery, mean (SD), min	172.1 (83.7)	156.6 (87.9)	.45
Surgical procedure			
Thoracic	5 (15.2)	11 (28.9)	.17
Abdominal	28 (84.8)	27 (71.1)	
Postoperative mechanical ventilation	15 (45.5)	14 (36.8)	.46
Duration of postoperative ventilation, median (IQR), h	34 (15-45)	23 (16-45)	.43
Surgical stress score, median (IQR)	10 (9-11)	10 (9-11)	.75
PRISM3, median (IQR)	2 (0-4.5)	3.0 (0-5.0)	.91
PIM2, median (IQR), % risk of mortality	1.3 (0.6-1.9)	1.4 (0.7-2.4)	.34

Abbreviations: IQR, interquartile range; PIM2, Pediatric Index of Mortality 2; PRISM3, Pediatric Risk of Mortality 3.

**Study End Points**

The cumulative morphine dose in the paracetamol group was 66% (95% CI, 34% to 109%) lower than that in the morphine group (median, 121 [IQR, 99-264] μg/kg per 48 hours vs 357 [IQR, 220-605] μg/kg per 48 hours; *P* < .001) (TABLE 2, FIGURE 2). Considering the 2 stratified age groups separately, the cumulative morphine dose in the paracetamol group was 49% (95% CI, -6% to 89%) lower than that in the morphine group for the neonates (aged 0 through 10 days) (median, 111 [IQR, 96-169] μg/kg per 48 hours vs 218 [IQR, 186-294] μg/kg per 48 hours; *P* = .002) and 73% (95% CI, 30% to 114%) lower for the older infants (aged 11 days to 1 year) (median, 152 [IQR, 112-346] μg/kg per 48 hours vs 553 [IQR, 361-765] μg/kg per 48 hours; *P* < .001).

The total morphine rescue dose did not differ significantly between the paracetamol and morphine groups (median, 25 [IQR, 0-164] μg/kg per 48 hours vs 20 [IQR, 0-226] μg/kg per 48 hours; *P* = .99). The amount or number of morphine rescue doses, and the number of patients requiring rescue doses, also did not differ (Table 2).

We found no significant differences for percentage of adverse effects between treatment groups (27.3% for paracetamol vs 34.2% for morphine; odds ratio, 0.9 [95% CI, 0.3 to 2.6]) (Table 2). Naloxone was administered 3 times in the morphine group and not at all in the paracetamol group. No seizures, hypotension, or gastrointestinal adverse effects occurred.

The median NRS-11 and mean COMFORT-B scores were similar in both groups (1 [IQR, 0-1] vs 1 [IQR, 0-2]; *P* = .17) and 13.0 [SD, 2.0] vs 13.1 [SD, 2.1]; *P* = .80, respectively).

**COMMENT**

This randomized controlled trial shows that infants who receive intravenous paracetamol as primary analgesic after major surgery require significantly less morphine than those who receive a continuous morphine infusion. Judging from the rescue morphine doses, a similar level of analgesia was obtained in either group. These results suggest that intravenous paracetamol may be an interesting alternative as primary analgesic in neonates and infants.

The opioid-sparing potential of paracetamol was shown in older children and adults. Hong et al<sup>11</sup> found a fentanyl-sparing effect of intravenous paracetamol in infants aged 6 to 24 months using parent- or nurse-controlled analgesia after ureteroneocystostomy. In older children, Korpela et al<sup>25</sup> showed that a single dose of 40 or 60 mg/kg of rectal acetaminophen has a clear morphine-sparing effect in outpatient surgery for older children, if administered during the induction of anesthesia. A recent systematic review showed a morphine-sparing effect of paracetamol (oral, rectal, or intravenous) in adult patients receiving morphine as postoperative patient-controlled analgesia. The reduction of morphine requirements was lower than in our study (14% vs 66%).<sup>26</sup>

In contrast, other studies did not find a morphine-sparing effect of rectal paracetamol, either in young infants (0-2 months)<sup>10</sup> or in older children.<sup>27-29</sup> We speculate that type of study design may partly explain the contrasting findings. In most studies baseline standard opioid infusions were administered in both study groups,<sup>10,11,29</sup> potentially blurring the actual effect of paracetamol. In our study, apart from the intraoperative morphine loading dose, paracetamol was given as primary analgesic with morphine rescue as a possibility. Furthermore, differences in paracetamol formulations used may result in variable absorption and plasma concentrations. These limitations are overcome by the intravenous administration in our study.

**Table 2.** End Points in First 48 Postoperative Hours

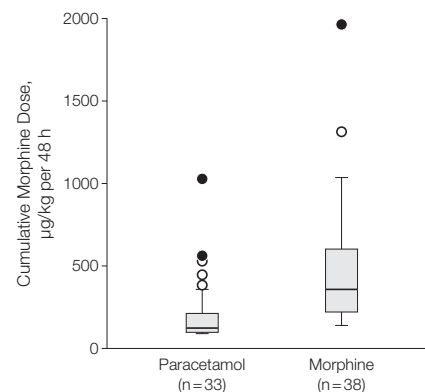
End Point	No. (%)		P Value	OR (95% CI)
	Paracetamol (n = 33)	Morphine (n = 38)		
Cumulative morphine dose, median (IQR), $\mu\text{g}/\text{kg}$	121 (99-264)	357 (220-605)	<.001	
Rescue morphine dose, median (IQR), $\mu\text{g}/\text{kg}$	25 (0-164)	20 (0-226)	.99	
Rescue morphine doses and infusions, median (IQR), No.	2 (0-6)	2 (0-5)	.97	
Patients receiving rescue morphine	22 (66.77)	23 (60.5)	.59	
Comedication				
Midazolam	5 (15.2)	3 (7.9)	.34	
Fentanyl	0	1 (2.6)	.35	
Vecuronium	1 (3.0)	0	.28	
Locoregional block	0	3 (7.9)	.10	
Adverse events				
Any adverse event	9 (27.3)	11 (28.9)		0.9 (0.3-2.6)
Reintubation	1 (3.0)	2 (5.3)		0.6 (0.1-6.5)
Apnea	4 (12.1)	10 (26.3)		0.5 (0.1-1.9)
Apnea with naloxone	0	3 (7.9)		0.5 (0.4-0.7)
Bradycardia	6 (18.2)	7 (18.4)		1.0 (0.3-3.3)
Urinary retention <sup>a</sup>	1	0		0.5 (0.4-0.6)

Abbreviations: IQR, interquartile range; OR, odds ratio.

<sup>a</sup>Twenty-six patients in the paracetamol group and 31 in the morphine group had a urinary catheter in place.

Paracetamol did not induce respiratory depression, an adverse effect observed in 3 patients in the morphine group. Despite a lack of statistical significance for this and other adverse effects, this observation does suggest a potential reduction in respiratory depression with use of paracetamol. The systematic review in adults also found no significant reduction in morphine-related adverse effects, despite a reduction in cumulative morphine dose administered postoperatively.<sup>26</sup> This phenomenon may be explained by a lack of power, because most studies were designed to detect a difference in efficacy but not in adverse effects. Also, in many studies, adverse effects are not systematically reported.<sup>26</sup>

A reduction of opioid-related adverse events may be mitigated by an increased risk of paracetamol-related adverse events. Using the dosing regimen of this study, plasma concentrations are expected to be similar to those obtained with rectal acetaminophen dosing.<sup>30,31</sup> Therefore, although evidence of safety specifically for intravenous paracetamol in neonates is limited,<sup>32</sup> it is unlikely that it is associated with

**Figure 2.** Cumulative Morphine Dose for Morphine and Paracetamol Study Groups Over 48 Postoperative Hours

Boxes indicate medians (horizontal lines) and interquartile ranges; error bars, 10th and 90th percentiles. Open black circles indicate outliers with values more than 1.5 times the height of the boxes; solid black circles, extreme outliers with values more than 3 times the height of the boxes. Two extreme outliers were identified in the paracetamol group, the first a boy aged 68 days who underwent surgery for long-gap esophageal atresia and subsequently needed a chest tube for a pneumothorax and the second a newborn boy with a gastroschisis for which a silo was placed. One extreme outlier was identified in the morphine group, a girl aged 355 days who underwent surgery for a recurrence of a congenital diaphragmatic hernia.

more toxicity than rectal paracetamol. The general safety of paracetamol in neonates and children has been widely documented.<sup>33</sup> More specifically, neonates have a lower risk of paracetamol-induced hepatotoxicity than have older children and adults because the enzymes (eg, CYP2E1) involved in the formation of N-acetyl-p-benzoquinone imine, the hepatotoxic metabolite, are still immature.<sup>34</sup> A systematic analysis of hepatotoxicity as adverse effect in pediatric trials of paracetamol could not confirm paracetamol-related toxicity when dosed therapeutically.<sup>35</sup>

Some limitations of our study need to be addressed. First, this is a single-center study in a strictly defined patient population. This may potentially limit ex-

ternal validity of the findings.<sup>36</sup> Second, as discussed above, this study was not powered to detect a difference in adverse effects, nor were we able to monitor liver function in the paracetamol group. This limits our ability to determine which treatment was safest.

In conclusion, among infants undergoing major surgery, postoperative use of intermittent intravenous paracetamol compared with continuous morphine resulted in a lower cumulative morphine dose over 48 hours.

**Author Contributions:** Dr Tibboel had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Ceelie and de Wildt contributed equally to this work. **Study concept and design:** Ceelie, de Wildt, van Dijk, van den Berg, Knibbe. **Acquisition of data:** Ceelie, van den Berg, van den Bosch, de Leeuw, Tibboel.

**Analysis and interpretation of data:** Ceelie, de Wildt, van Dijk, van den Berg, Duivenvoorden, Mathôt, Knibbe.

**Drafting of the manuscript:** Ceelie, van Dijk, van den Berg.

**Critical revision of the manuscript for important intellectual content:** de Wildt, van Dijk, van den Bosch, Duivenvoorden, de Leeuw, Mathôt, Knibbe, Tibboel. **Statistical analysis:** Ceelie, van Dijk, Duivenvoorden. **Obtained funding:** de Wildt, Knibbe, Tibboel.

**Administrative, technical, or material support:** Ceelie, van den Berg, van den Bosch, de Leeuw, Mathôt. **Study supervision:** de Wildt, van Dijk, Knibbe, Tibboel.

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